REMARKS

Claims 1 and 3-12 were presented and stand rejected. Claims 2 and 13-21 have been canceled pursuant to a restriction requirement imposed by the Office. Claim 1 has now been amended to reflect the restriction requirement. Claims 5 and 6 have been amended to correct an incorrect dependency. No new matter is added by these amendments; entry of the amendments and reconsideration of the claims in light of the amendments and the following comments are respectfully requested.

Restriction Requirement

The Office imposed a restriction requirement, and the Applicant amended the claims in response and provisionally elected the subject matter of Group I while explaining why the restriction requirement was improper. The Office asserts that the restriction requirement was not traversed. This was not the Applicant's intent, as evident from the applicant's request for reconsideration in the response, and the statement that the election of Group I was made 'provisionally'. Indeed, the applicant amended the claims to incorporate the subject matter of Group II into claim 1 along with the subject matter of Group I, and stated that the same invention is claimed in both groups.

The Applicant further pointed out that "the principle of the invention is the same, regardless of whether the protective formyl group is attached to the α-aminonitrile or the reaction is run in reverse, using the unprotected form..." As one of ordinary skill would recognize, Group I and Group II are the forward and the reverse directions of a single enzymatic reaction. The applicant pointed out that, regardless of whether the reaction is run in the forward or reverse sense, the same enzyme is used to perform the reaction. And of course the starting material for running in one direction is the product of running in the other direction, and vice versa: the enzyme catalyzes reactions toward an equilibrium, and as is well known, the position of the equilibrium can be controlled by adjusting the reaction conditions—e.g., adding a formylating reagent to favor formylation.

The Applicant further pointed out that, before the preliminary amendment that was entered solely to eliminate multiply-dependent claim format, claims 4-12 depended from both claim 1, describing the de-acylation reaction (Group I), and claim 2, describing the acylation reaction (Group II). Therefore, the Applicant believes that the restriction requirement was timely traversed and that one of ordinary skill would understand that Groups I and II represent a single inventive concept: as the response to the restriction requirement stated, "there is only one invention". The Applicant does not believe the previous response can accurately be described as an election without traverse, and believes that the restriction requirement should have been reconsidered by the Office and should have been withdrawn.

The claims as submitted in the amendment accompanying the response to the restriction requirement included the subject matter of both Groups I and II. It appears that the Office nevertheless entered those claims. The applicant has now amended claim 1 to omit the subject matter of Group II (the acylation, or 'reverse' direction of the enzymatic reaction), solely to advance prosecution. Nevertheless, the Applicant believes that the restriction requirement was traversed by the above statements pointing out the common technical features and inventive principle of the subject matter of Groups I and II. Respectfully, the Applicant again requests reconsideration of the restriction requirement.

Rejections under 35 U.S.C. § 112, 2nd Paragraph

Claims 5 and 6 were alleged to be indefinite because the limitation "peptide deformylase" does not find antecedent basis in claim 1. The Examiner correctly observed that these claims should both depend from claim 4. The Applicant appreciates the suggestion and has corrected that dependency in the amended claim list.

Rejections under 35 U.S.C. § 112, 1st Paragraph

Claims 1 and 3-12 stand rejected for alleged failure to describe the genus of acylases or peptide deformylases mentioned in the claim. The Applicant traverses this rejection as improperly requiring a structural description of an unclaimed species that is conventional in the art.

The written description requirement demands only a detailed description of that which is novel, and sufficient detail to convey to one of ordinary skill that the applicant was in possession of the claimed invention. According to the Guidelines for examination of the Written Description requirement in the MPEP § 2163, "That which is conventional or well-known to one of ordinary skill in the art need not be disclosed in detail." See Hybritech Inc. v. Monoclonal Antibodies, 231 USPQ at 94 (Fed. Cir. 1986). Claims in *Eli Lilly*, for example, did not satisfy the written description requirement because the claims did not describe by structure the chemical species, where the chemical species was the novel feature of the claim. University of California v. Eli Lilly, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997). But the presence of a chemical entity in a method claim not necessarily demand a structural definition of that entity, just as the presence of a computer in a method claim does not require a structural description of the computer and all of its parts: the question is, would one of ordinary skill understand from the application as filed that the applicant was in possession of the claimed invention.

Enzymes are not the claimed invention here. All of the claims are drawn to methods of using certain enzymes for the preparation of α –aminonitriles and/or N-formyl α -aminonitriles with enhanced optical purity: the Applicant is not claiming Enzymes, only methods of using them to partially resolve racemic mixtures of α-aminonitriles. Thus no description of the enzymes by structure or sequence is required. The enzymes used in these methods are typically well-known in the art, so a detailed description of the enzymes is not required by *Eli Lilly* or its progeny. Acylases comprise a well-known class of enzymes. One of ordinary skill would understand the term acylase to be a description of a genus of enzymes by their function; that is the typical way enzymes are described by those in the art, and they would understand the functional description to include enzymes that transfer an acyl group. Also, the Applicant has provided in the specification a more detailed description, using examples: penicilline acylase, Pen-G acylase, Pen-V acylases, metalloproteases, esterases, deacetylases, and particularly peptide deformylases. Specification, pg 3, lines 11-15. Each of these is an art-recognized class of enzymes, and each is a term that is well understood by those skilled in the art. Thus this description of the class of enzymes to be used in

the process satisfies the written description requirement for the method claims presented, because one of ordinary skill would understand which enzymes are appropriate for use.

Furthermore, as applied to claims 4-9, which recite a peptide deformylase, the Office overlooks extensive additional description in the specification of particular peptide deformylase enzymes suitable for use in the methods of the invention. The specification describes these based on their detailed substrate preferences at page 3, lines 16-30, including a quantitative description of the relative activity level of the enzyme with different substrates. It also provides other names used for peptide deformylases (pg 3, line 36 to pg 4, line 3) and describes the preferred classes as those of E.C. 3.5.1.27 and 3.5.1.31 (pg 4, line 4 to line 18): this is a description based on the standard Enzyme Commission nomenclature used routinely in the art to describe enzymes. The specification further provides a description of the members of the class by size and common fold (pg. 4, line 19 to line 24). Finally, it describes three highly conserved sequences found in many peptide deformylases (pg. 4, lines 24 to 34), citing a 1998 Journal of Biological Chemistry reference, and it specifies several eubacteria from which these enzymes can be obtained (pg. 4, line 36 to pg 5, line 7). The enzymes to be used in the claimed methods are thus described just as they would ordinarily be described by those of skill in the art: one of ordinary skill does not require a structural description of an enzyme to recognize that it can be used for a described function, and the Applicant is not attempting to claim any of the enzymes. Thus for claims 1 and 3, and particularly for claims 4-9, there is more than ample detail for one of ordinary skill to recognize that the Applicant was in possession of the claimed methods, and to recognize what enzymes could be used to practice those methods.

Rejections under 35 U.S.C. § 103

The Office alleges that claims 1 and 3 are obvious over Romeo, in view of Drummond. Romeo discloses a process whereby benylpenicillin acylase cleaves a phenylacetyl group from various amides; among the amides are several N-phenylacetyl α-aminonitriles. The resultant products thus include α-aminonitriles, some of which have some optical activity; thus the method provides at least partial enhancement of the optical activity of an α-aminonitrile. The Office

concedes that Romeo does not disclose a formylating agent, but asserts that the formylating agent mentioned in Drummond provides this element. Specifically, the Office said, "it would have been obvious...to modify the method of Romeo et al. such that N-phenylacetyl-aminobutyronitrile isomer produced by the action of the *E. coli* benzylpenicillin acylase is contacted with the formic acid (formylating agent) as taught by Drummond et al." This appears to propose that an enzymatic formylation reaction would be used on the N-phenylacetyl compounds of Romeo with the formylating reagent of Drummond.

The Office has the burden of providing a *prima facie* case of obviousness before the Applicant needs to provide rebuttal. To establish a *prima facie* case of obviousness, the Office must demonstrate that the references disclose all elements of the claimed invention literally or by equivalence; that the references or the ordinary skill in the art provides motivation to combine the elements to produce the claimed invention; and that one of ordinary skill would reasonably expect the combination to operate. The Office has not met this burden.

First, the Office has not shown all of the elements of the claimed invention. The Romeo reference utilizes benzylpenicillin acylase to cleave a phenylacetyl group. The Office asserts that Drummond provides a formylating agent, suggesting that one of ordinary skill would be motivated to use the formylating agent of Drummond somehow in the method of Romeo. However, there is a critical feature missing: claim 1 recites that the α-aminonitrile is in the N-formyl form. The references do not provide an N-formyl α-aminonitrile, nor do they demonstrate how to make one or suggest that one is desirable. Perhaps the Office intended to assert that the enzyme of Romeo could be used in the acylating (reverse) direction with the formylating agent of Drummond to make an N-formyl α-aminonitrile? If so, surely this supports the Applicant's assertion that the Group I and Group II reactions are a single invention and should not be restricted apart.

Furthermore, if the claims are restricted Group I as previously stated, there is no role for a formylating agent at all: the Group I invention provides partial resolution of the racemic N-formyl compound based on de-formylation of an N-formyl α-aminonitrile. Only the invention of Group II, which is the reverse reaction, requires a formylating agent. Thus if the restriction requirement is

maintained, the Drummond reference is irrelevant to the claims, and an obviousness rejection clearly cannot be sustained based on Romeo alone, as the Office concedes.

The Applicants requested reconsideration and withdrawal of the restriction requirement, which would render Drummond relevant; therefore, the Applicant will further respond as though that has been done, in the interest of compact prosecution. Assuming the reaction of Group II is included, the formylating agent of Drummond is relevant to the obviousness analysis with respect to the formylation reaction, which requires a formylating agent.

Still, the combination of references is not sufficient to provide a reasonable expectation of success with the combination of features. One of ordinary skill might recognize that the de-acylation reaction taught in Romeo is reversible; however, nothing in Romeo or Drummond would provide a reasonable expectation of success with that enzyme for formylation. At most, Romeo would suggest that the reverse reaction might work with a phenylacetylating reagent, which is a very different structure from a formylating reagent. The enzyme in Romeo is only disclosed to be capable of de-acylating an N-phenylacetyl amide, and from its name it must process some type of benzylpenicillin substrate(s); however, the references provide no reason to expect it to utilize formic acid as an acylating agent to formylate an α-aminonitrile. Enzymes are typically somewhat discriminating with respect to substrates; and the references do not teach anything about the scope of the substrate recognition of the acylase employed that would suggest it could function to formylate or deformylate any substrate. Thus one would not find in these references any reasonable expectation of success with using the Drummond formylating agent in any method of Romeo.

Finally, nothing in the references provides motivation to even <u>try</u> to make an N-formyl α-aminonitrile. The Office asserts that one would be motivated to do so "for the purposes of producing a beneficial method that can synthesize formylated N-phenylacetyl-aminobutyronitrile isomers." Respectfully, nothing in the references suggests that the enzyme would formylate any substrate, and nothing in the references suggests the desirability of making an N-formyl derivative. The cited references are simply silent on the subject, other than Drummond's formylation of a folate derivative, which cannot be relevant to the claimed invention. Thus the Office cannot provide a

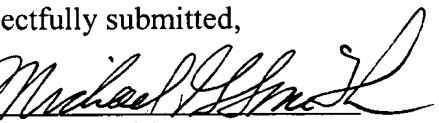
prima facie case of obviousness based on these references, even if the restriction requirement is withdrawn. Withdrawal of this rejection is therefore requested.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Office is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Office is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.*. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 16, 2005

Respectfully submitted,

By 

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